PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 16397/WO/03	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL 03/00569	International filing date *(day/month/year)* 09.07.2003	Priority date *(day/month/year)* 09.07.2002
International Patent Classification (IPC) or both national classification and IPC A61M1/36		
Applicant THERA-SONICS ULTRASOUND TECHNOLOGIES LTD et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 11 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.01.2004	11.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Böttcher, S Telephone No. +49 89 2399-2875

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL 03/00569

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-62 as originally filed

Claims, Numbers

1-48 filed with telefax on 28.09.2004

Drawings, Sheets

1/19-19/19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 16-18

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 16-18

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15,19-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-15,19-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15,19-27
	No:	Claims	

2. Citations and explanations

   see separate sheet

1. Reference is made to the following documents:

   D1: US-A-5 022 899
   D2: WO-A-01/41655

2. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. The features concerned are the following:

   - "said ultrasonic waves pushing said particles in the direction of a friction layer (...) thereby causing the motion of said particles to stop" (step a),
   - "said ultrasonic waves (...) causing said particles to be held in place..." (step a),
   - "thereby surrounding said particles with an asymmetric acoustic radiation force and causing fragmentation (...) into smaller ones" (step i),
   - "which alternately compresses and releases said particles, thereby increasing..." (step ii).

   These definitions leave completely open, which technical requirements are necessary in order to achieve the desired effects. Consequently, these features can not be used to distinguish the subject-matter of the claim from the prior art.

   Since these results, especially the fragmentation of the particles into smaller particles and the increase of the efficiency of the diffusion of material, is **not** one which can be directly and positively verified by tests involving nothing more than trial and error, such definitions have to be objected to with respect to Article 6 PCT (see also PCT Guidelines, III-4.7).

   The same objection applies, mutatis mutandis, to the corresponding independent claim 28, which therefore is also considered not clear.

3. The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses:

   A method for neutralizing acoustically active particles immersed in a flowing fluid, in which ultrasonic waves are provided, which propagate through said fluid, and an

acoustic radiation force is provided.

The subject-matter of claim 1 differs from this known method in that in addition to the ultrasonic waves an acoustic radiation field is provided which is either modulated at a specific frequency or pulsating or both.

The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as facilitating the fragmentation or the reduction of the particles through a deformation process or a diffusion process.

The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) since a method using a frequency modulated or a pulsating acoustic radiation field is neither disclosed nor rendered obvious by the available prior art.

Claims 2-15 and 19-27 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

4. The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claim 28, which therefore is also considered to meet the requirements of the PCT with respect to novelty and inventive step.

Claims 29-48 are dependent on claim 28 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

Claims

1. A method for selectively slowing the motion of acoustically active particles immersed in a flowing fluid, eventually stopping their motion, holding them in place by pushing them against a surface or against the flow of said flowing fluid, and/or breaking up said acoustically active particles into smaller particles and/or dissolving them comprising the following steps:

(a) exposing said acoustically active particles suspended in said fluid to ultrasonic waves propagating through said fluid;

(b) pushing said particles in the direction of propagation of said ultrasonic waves by means of the acoustic radiation force exerted by said waves;

(c) slowing and/or stopping the motion of said acoustically active particles as they enter a friction layer near a surface or surfaces ; and

(d) providing an acoustic radiation force having a temporal waveform to act on said acoustically active particles, thereby breaking up said ultrasonically active particles into particles having smaller size and/or causing said particles to dissolve in said fluid.

2. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for breaking up are provided by the same source.

3. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for breaking up are provided by different sources.

4. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for breaking up are applied as a superimposition of acoustic radiation forces having two or more frequencies and or waveforms.

5. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for breaking up have waveforms chosen from the group comprising, but not limited to:

(a) continuous; and

(b) pulsating.

6. A method according to claim 1, further comprising the steps of:

(i) after step (a), aiming the ultrasonic waves towards the surface of a wall of the vessel containing the fluid or a surface placed in their path;

(ii) after step (b), reducing the speed of the acoustically active particles, which is equal to that of the fluid surrounding them as they are progressively pushed into regions of said fluid closer to said surface; and

(iii) after step (c), pushing said acoustically active particles against said surface by means of the force exerted by said acoustic radiation, thus creating frictional forces between said surface and said acoustically active particles which prevent the movement of said particles and pulsating compressional forces that cause said acoustically active particles to dissolve in said fluid.

7. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for breaking up are aimed in a direction opposite to the direction of flow of the fluid and along the axis of the vessel through which said fluid flows.

8. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for breaking up are focused.

9. A method according to claim 1, wherein the acoustic radiation force for pushing and/or the acoustic radiation force are generated upon detection of the acoustically active particles by a detector or detectors.

10. A method according to claim 9, wherein the detector is chosen from the group comprising, but not limited to:

(a) an ultrasonic detector; and

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(b) an electro-optic detector.

11. A method according to claim 9, wherein the detection is made by detecting ultrasonic energy sourced emitted by an ultrasonic transducer, refracted by the particles, and detected by said transducer.

12. A method according to claim 9, wherein the detection is made by detecting ultrasonic energy sourced emitted by an ultrasonic transducer, refracted by the particles, and detected by a different transducer.

13. A method according to claim 1, wherein the flow of the fluid is through a vessel that is open to view.

14. A method according to claim 1, wherein the flow of the fluid is through a vessel that is surrounded by an object and therefore is not open to view.

15. A method according to claim 14, wherein the orientation of the vessel is determined with the aid of ultrasonic detectors which detect the flow of fluid through said vessel.

16. A method according to claim 15, wherein the external object is a human body.

17. A method according to claim 16 wherein the vessel is a blood vessel.

18. A method according to claim 16 wherein the vessel is the carotid artery.

19. A method according to claim 1, wherein the surface is one or a plurality of membranes surface upon which large acoustically active particles break apart upon impact into smaller particles that pass through the openings in said membranes.

20. A method according to claim 19, wherein the size of the pores in the membranes is between0.1 μm to 1mm.

21. A method according to claim 19 wherein the membranes together with the ultrasonic propagating field acting on the acoustically active particles acts as a semi-permeable membrane which permits particles to leave the fluid flow through the pores of said membranes and prevents the particles from reenter the flow.

22. A method according to claim 19, wherein there is an array of open cells on the side of the membrane surface opposite to the flow of the acoustically active particles and wherein after broken apart particles pass through the openings, they enter said cells thus preventing them from recombining to form particles whose dimensions exceed that of said cells.

23. A method according to claim 1, wherein the surface comprises an array of cells arranged in a honeycomb pattern.

24. A method according to claim 19, wherein the pressure exerted on acoustically active particles larger than the pore size of the membrane causes them to deform without breaking apart upon impact with said membrane and slip through said pores, regaining their original shape after slipping through said membrane.

25. A method according to claim 19 where the dimensions of the pores of each succeeding membrane in a plurality of membranes become smaller in the direction of the fluid flow.

26. A method according to claim 1, wherein the acoustically active particles comprise an encapsulated material.

27. A method according to claim 26, wherein the encapsulated material is a drug.

28. An ultrasonic system for selectively slowing the motion of acoustically active particles immersed in a flowing fluid, eventually stopping their motion, holding them in place by pushing them against a surface or against

the flow of said flowing fluid, and breaking up said acoustically active particles into smaller particles and/or dissolving them, the apparatus comprising:

(a) a fluid flow path through a vessel;

(b) acoustically active gaseous or fluid particles immersed in the flowing fluid;

(c) a surface which creates a friction layer to the fluid that flows adjacent to it, and can be partially or fully submerged in the fluid, or may consist of a wall of said vessel or a type of membrane;

(d) Transducing means acoustically connected to said vessel or submerged in it;

wherein:

- said transducing means delivers acoustic energy having sufficient power to accelerate said acoustically active particles towards said surface where their motion relative to said flowing fluid ceases and to cause breaking apart of said acoustically active particles on said surface;

- said acoustic energy being modulated at the optimal deformation frequency of said acoustically active particles, thereby causing safe and selective breakage of said particles into smaller particles which naturally dissolve faster than large particles;

- said acoustic energy being superimposed by harmonic frequencies thereby achieving a negative rectified diffusion of

substance from inside the particle to the said fluid, or at least lowering the rectified diffusion particles, thus reducing the risk of jet streams and cavitations.

29. A system according to claim 28, wherein the surface is a layer of the flowing fluid and the acoustic energy is directed opposite to the direction of flow.

30. A system according to claim 28, wherein the acoustic energy is focused.

31. A system according to claim 29, wherein the fluid flows in a tube.

32. A system according to claim 28, wherein the transducing means comprise an ultrasound head comprising one or more ultrasound transducers.

33. A system according to claim 32, wherein the number of ultrasound transducers is at least three and two of said transducers are used to detect the presence of acoustically active particles and to influence the operation of the remainder of said transducers.

34. A system according to 32, wherein the transducing means are comprised of a disc shaped main transducer surrounded by an outer ring shaped

transducer, said outer transducer being driven in an anti-phase manner to said main transducer.

35. A system according to claim 32, wherein the acoustic energy is focused.

36. A system according to claim 32, wherein the acoustic energy is unfocused.

37. A system according to claim 28, wherein the system comprises means for providing ultrasonic energy for selectively stopping, breaking apart, shrinking, and dissolving acoustically active particles immersed in blood flowing in the carotid arteries.

38. A system according to claim 37, further comprising a disposable pillow.

39. A system according to claim 37, wherein the system comprises two ultrasonic heads one located on each carotid artery.

40. A system according to claim 37, comprising two ultrasonic heads each comprising at least two ultrasonic bubble detectors for detect acoustically active particles and/or fluid flow and at least one ultrasonic transducer to provide the ultrasonic energy.

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41. A system according to claim 28, wherein the surface is a membrane or has a honeycomb structure to aid in breaking apart and/or holding the acoustically active particles.

42. A system according to claim 41, wherein the membrane acting together with the acoustic energy acts as a semi-permeable membrane, which acts to remove acoustically active particles from the flowing fluid in which they are immersed.

43. A system according to claim 28, wherein the vessel through which the fluid flows is arterial lines of cardiopulmonary machines, contrast media catheters, and dialysis machines and high-flow venous lines.

44. A system according to claim 28, wherein the acoustically active particles comprise encapsulated material.

45. A system according to claim 44, wherein the acoustically active particles are delivered to a selected location in a vessel by the flowing fluid, concentrated at said location within said vessel and the encapsulated material is released at said location by shrinking and/or breaking apart and/or dissolving said particles.

46. A system according to claim 45, wherein the acoustically active particles are introduced into the flowing fluid using a specially designed balloon catheter.

47. A system according to claim 44, wherein the encapsulated material is a drug.

48. A system according to claim 45, wherein the vessel is part of the vascular system of a human or animal body.